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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450 Alexandria, VA 22313 on July 6, 2005.

Doran R. Pace, Patent Attorney

REQUEST FOR CERTIFICATE OF CORRECTION UNDER 37 CFR 1.322
Docket No. GJE-89
Patent No. 6,908,736

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Daniel Henry Densham
Issued	:	June 21, 2005
Patent No.	:	6,908,736 B1
For	:	DNA Sequencing Method

Mail Stop Certificate of Corrections Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CERTIFICATE OF CORRECTION
UNDER 37 CFR 1.322 (OFFICE MISTAKE)

Sir:

A Certificate of Correction (in duplicate) for the above-identified patent has been prepared and is attached hereto.

In the left-hand column below is the column and line number where errors occurred in the patent. In the right-hand column is the page and line number in the application where the correct information appears.

Patent Reads:	**Application Reads:**
Column 8, line 67 to Column 9, line 1:	Amendment dated January 7, 2005, page 2 (original claim 22, last two lines; renumbered as claim 1):
"presence of poly nucleotide monomers, the polynucleotide monomers do not"	--presence of nucleotide monomers, the nucleotide monomers do not--

Column 9, line 13:	Preliminary Amendment dated April 3, 2002, page 2 (original claim 28, line 2; renumbered as claim 6):
"infraction"	--interaction--
Column 10, line 21:	Amendment dated January 7, 2005, page 4 (original claim 46, line 2; renumbered as claim 15):
"one FRET: fluorescence"	--one fluorescence--.

A true and correct copy of Applicant's Preliminary Amendment dated April 3, 2002 and Amendment Under 37 CFR §1.116 dated January 7, 2005, which support Applicant's assertion of the errors on the part of the Patent Office accompanies this Certificate of Correction.

Approval of the Certificate of Correction is respectfully requested.

Respectfully submitted,

Doran R. Pace
Patent Attorney
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Phone No.: 352-375-8100
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Address: P.O. Box 142950
Gainesville, FL 32614-2950

DRP/sl
Attachments: Certificate of Correction; Preliminary Amendment dated April 3, 2002; Amendment Under 37 CFR §1.116 dated January 7, 2005.

April 3, 2002

PRELIMINARY AMENDMENT
Patent Application
Docket No. GJE-89

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Daniel Henry Densham

Docket No. : GJE-89

For : DNA Sequencing Method

Box PCT
Assistant Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Sir:

It is respectfully requested that the above-identified patent application be amended as follows:

In the Specification

After page 15: Please insert as new page 16 the attached Abstract of the Disclosure.

In the Claims

Please cancel claims 1-21, without prejudice.

Please add the following new claims 22-45:

22. A method for determining the sequence of a polynucleotide, comprising the steps of:

i. reacting a target polynucleotide with an enzyme that is capable of interacting with and processing along the polynucleotide, under conditions sufficient to induce enzyme activity; and

ii. detecting conformational changes in the enzyme as the enzyme processes along the polynucleotide.

23. The method according to claim 22, wherein the enzyme is a polymerase enzyme.

24. The method according to claim 22, wherein the enzyme is a helicase enzyme or a primase enzyme.

25. The method according to claim 22, wherein the enzyme is immobilised on a solid support.

26. The method according to claim 25, comprising a plurality of enzymes immobilised on the solid support.

27. The method according to claim 22, wherein the enzyme comprises a first bound detectable label, the characteristics of which alter as the enzyme undergoes a conformational change.

28. The method according to claim 27, wherein the enzyme comprises a second bound detectable label capable of interacting with the first label, wherein the degree of interaction is dependent on a conformational change in the enzyme.

29. The method according to claim 27, wherein a second detectable label is bound to a nucleotide brought into contact with the enzyme.

30. The method according to claim 28, wherein the first label is an energy acceptor and the second label is an energy donor, or wherein the first label is an energy donor and the second label is an energy acceptor, and wherein step (ii) is carried out by measuring energy transfer between the two labels.

31. The method according to claim 29, wherein the first label is an energy acceptor and the second label is an energy donor, or wherein the first label is an energy donor and the second label is an energy acceptor, and wherein step (ii) is carried out by measuring energy transfer between the two labels.

32. The method according to claim 22, wherein step (ii) is carried out using confocal microscopy.

33. The method according to claim 32, wherein step (ii) is carried out by fluorescence imaging.

34. The method according to claim 27, wherein step (ii) is carried out by measuring a polarisation effect consequent on the altered characteristics of the first label.

35. The method according to claim 34, wherein step (ii) is carried out by fluorescence polarisation anisotrophy.

36. A method for determining the sequence of a polynucleotide, comprising detecting via fluorescence resonance energy transfer a conformational change in an enzyme that interacts with and processes along a target polynucleotide, thereby permitting determining the sequence of the polynucleotide.

37. The method according to claim 36, wherein the enzyme is a polymerase enzyme.

38. The method according to claim 36, wherein the enzyme is immobilised on a solid support.

39. The method according to claim 37, wherein the enzyme is immobilised on a solid support.

40. A method for determining the sequence of a polynucleotide, comprising detecting a detectably-labelled enzyme that is capable of interacting with and processing along a target polynucleotide, wherein the label alters its detectable characteristics as the enzyme processes along the polynucleotide, thereby permitting determining the sequence of the polynucleotide.

41. A solid support comprising at least one immobilised enzyme capable of interacting with and processing along a target polynucleotide, the enzyme being labelled with one or more detectable labels.

42. The solid support according to claim 41, wherein the enzyme is a polymerase.

43. The solid support according to claim 41, wherein the label is a fluorophore.

44. The solid support according to claim 42, wherein the label is a fluorophore.

45. A system for determining a sequence of a polynucleotide, comprising a solid support according to claim 41, and an apparatus for detecting the label.

Remarks

Support for the new claims presented herein can be found throughout the subject specification and claims 1-21 as filed.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Respectfully submitted,

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DRP/sl
Attachment: Abstract of the Disclosure

Abstract of the Disclosure

The present invention pertains to a method for determining the sequence of a polynucleotide, the method relying on the detection of a conformational change in an enzyme that interacts with and processes along the polynucleotide. The detection of a conformational change may be carried out by measuring changes in a fluorophore bound to the enzyme.

I hereby certify that this correspondence is being facsimile transmitted to the United States Patent and Trademark Office on January 7, 2005.

Doran R. Pace, Patent Attorney

AMENDMENT UNDER 37 CFR §1.116
Examining Group 1637
Patent Application
Docket No. GJE-89
Serial No. 10/089,877

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Cynthia B. Wilder, Ph.D.
Art Unit	:	1637
Applicant	:	Daniel Henry Densham
Serial No.	:	10/089,877
Filed	:	April 3, 2002
Conf. No.	:	1425
For	:	DNA Sequencing Method

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

AMENDMENT UNDER 37 CFR §1.116

Sir:

A Petition and Fee for a one-month Extension of Time through and including January 7, 2005, accompanies this Amendment.

In response to the Office Action dated September 7, 2004, please amend the above-identified patent application as follows:

In the Claims

1-21 (canceled)

22 (currently amended). A method for determining the sequence of a polynucleotide, comprising the steps of:

i. reacting a target polynucleotide with an enzyme that interacts with and processes along the polynucleotide, under conditions sufficient to induce enzyme activity; and

ii. detecting conformational changes in the enzyme as the enzyme processes along the polynucleotide, and thereby determining the sequence of the polynucleotide;

wherein the enzyme comprises a ~~first~~ bound fluorescent molecule, the characteristics of which alter as the enzyme undergoes a conformational change, and wherein the target polynucleotide does not comprise a label prior to, during, or after the enzyme processes along the polynucleotide, and wherein if step (i) is carried out in the presence of nucleotide monomers, the nucleotide monomers do not comprise a label.

23 (previously presented). The method according to claim 22, wherein the enzyme is a polymerase enzyme.

24 (previously presented). The method according to claim 22, wherein the enzyme is a helicase enzyme or a primase enzyme.

25 (previously presented). The method according to claim 22, wherein the enzyme is immobilised on a solid support.

26 (previously presented). The method according to claim 25, comprising a plurality of enzymes immobilised on the solid support.

27 (canceled).

28 (currently amended). The method according to claim 22, wherein the enzyme comprises a bound label that interacts with the ~~first~~ bound fluorescent molecule, wherein the degree of interaction is dependent on a conformational change in the enzyme.

29 (canceled).

30 (currently amended). The method according to claim 28, wherein the ~~first~~ bound fluorescent molecule is an energy acceptor and the bound label is an energy donor, or wherein the ~~first~~ bound fluorescent molecule is an energy donor and the bound label is an energy acceptor, and wherein step (ii) is carried out by measuring energy transfer between the ~~first~~ bound fluorescent molecule and the bound label.

31 (canceled).

32 (previously presented). The method according to claim 22, wherein step (ii) is carried out using confocal microscopy.

33 (previously presented). The method according to claim 32, wherein step (ii) is carried out by fluorescence imaging.

34 (currently amended). The method according to claim 22, wherein step (ii) is carried out by measuring a polarisation effect consequent on the altered characteristics of the ~~first~~ bound fluorescent molecule.

35 (previously presented). The method according to claim 34, wherein step (ii) is carried out by fluorescence polarisation anisotrophy.

36-40 (canceled).

41 (currently amended). A solid support comprising at least one immobilised polymerase or helicase enzyme, the enzyme being labelled with at least one fluorescence resonance energy transfer (FRET) ~~FRET~~ donor label and at least one FRET acceptor label.

42 (canceled).

43 (currently amended). The solid support according to claim 41, wherein the at least one ~~FRET~~ fluorescence resonance energy transfer donor label is a fluorophore.

44 (canceled).

45 (currently amended). A system for determining a sequence of a polynucleotide, comprising a solid support ~~according to claim 41~~ comprising at least one immobilised polymerase or helicase enzyme, the enzyme being labelled with at least one fluorescence resonance energy transfer (FRET) donor label and at least one FRET acceptor label, and an apparatus for detecting the label.

46 (currently amended). The solid support according to claim 41, wherein the at least one ~~FRET~~ fluorescence resonance energy transfer acceptor label is a fluorophore.

Remarks

Claims 22-26, 28, 30, 32-35, 41, 43, 45, and 46 are pending in the subject application. Applicant gratefully acknowledges the Examiner's withdrawal of the objection and the previous rejections under 35 USC §§112, 102(b), 102(e), and 103(a). Applicant also gratefully acknowledges the Examiner's indication that claims 41, 43, 45, and 46 are free of the prior art. By this Amendment, Applicant has amended claims 22, 28, 30, 34, 41, 43, 45, and 46. Support for the amendments can be found throughout the subject specification and in the claims as originally filed. Claim 46, which referenced the solid support of claim 41, has been amended to recite all the elements and limitations of the solid support of claim 41. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 22-26, 28, 30, 32-35, 41, 43, 45, and 46 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

As an initial matter, Applicant would like to thank the Examiner for the courtesy of the telephonic conference conducted with Applicant's undersigned representative on December 15, 2004. Applicant respectfully submits that the amendments to the claims and the remarks presented herein are in accord with the substance of the telephonic conference in which the rejections under 35 USC §102 and §103 were discussed.

Claims 41, 43, 45, and 46 are rejected because of informalities. Specifically, the claims are objected to for using the abbreviation "FRET." In according with the Examiner's suggestion, claims 41, 43, and 46 have been amended to recite "fluorescence resonance energy transfer" with the abbreviation "FRET" in parentheses in claim 41. Accordingly, reconsideration and withdrawal of the objection, and an indication of allowance of the claims, is respectfully requested.

Claims 22-26, 28, 30, and 32-35 are rejected under 35 USC §112, second paragraph, as indefinite. Applicant respectfully asserts that the claims are definite. However, in regard to the rejection of claims 22-26, 28, 30, and 32-35 for the recitation of a "first" fluorescent molecule, Applicant has amended the claims to delete reference to "first" and to recite a "bound fluorescent molecule." This amendment is intended to clarify that the claimed method does not require multiple, distinct fluorescent molecules attached to the enzyme. However, it should be understood that the enzyme can also comprise, in addition to the "bound fluorescent molecule," a "bound label" as

provided in dependent claims 28 and 30. The "bound label" is distinct from the "bound fluorescent molecule" of the claimed subject matter and this is clear from the disclosure in the subject specification. In regard to the rejection of claims 28, 30, and 34 for lack of antecedent basis, Applicant has amended those claims to recite a "bound" fluorescent molecule in accord with the language in claim 22. The amendments presented herein have been made to lend greater clarity to the claimed subject matter. Accordingly, reconsideration and withdrawal of the rejection under 35 USC §112, second paragraph, is respectfully requested.

Claims 22, 23, 25,28, and 30 are rejected under 35 USC §102(e) as anticipated by Korlach *et al.* (Published U.S. Application 2003/0044781). In addition, claims 24, 26, 32, and 34 are rejected under 35 USC §103(a) as obvious over the Korlach *et al.* application in view of Chan *et al.* (U.S. Patent No. 6,210,896). Also, claim 33 is rejected under 35 USC §103(a) as obvious over Korlach *et al.* in view of Chan *et al.* (U.S. Patent No. 6,355,420) and claim 35 is rejected under 35 USC §103(a) as obvious over Korlach *et al.* in view of Ha *et al.* (1996). Applicant respectfully traverses each of these grounds of rejection.

Applicant respectfully asserts that the primary reference cited in each of the rejections, the Korlach *et al.* publication, does not teach or suggest the claimed invention. Moreover, the secondary references cited in the §103 obviousness rejections do not overcome the deficiencies or failings of the Korlach *et al.* reference and do not teach or suggest the elements of Applicant's claimed methods. The sequencing methods disclosed in the Korlach *et al.* publication all require the use of labeled nucleotides, whereas Applicant's claimed method does not require labeled nucleotides. In fact, in certain embodiments of Applicant's claimed methods, nucleotide monomers are not required at all (*e.g.*, where the polymerase is a helicase). Moreover, in Applicant's claimed method, the target polynucleotide is not labeled. In the methods disclosed in the Korlach *et al.* publication, labeled nucleotides are incorporated in the target polynucleotide for some period during enzyme processing (Applicant acknowledges that the Korlach *et al.* publication teaches that the label can be subsequently removed or cleaved from the nucleotide incorporated into the target polynucleotide). Thus, in the Korlach *et al.* methods, the target polynucleotide does comprise a label at some point or step during the method.

By this Amendment, Applicant has amended claim 22 to clarify that 1) individual nucleotide monomers, if utilized in the claimed method, are not labeled; and 2) that the target polynucleotide is not labeled prior to, during, or after enzyme processing along the target polynucleotide. Support for these amendments can be found throughout the subject specification and are implicit in the disclosure therein. It is well settled in patent law that the claim language of an amendment need not be disclosed word for word in a specification. *In re Wilder*, 222 USPQ 369, 372 (Fed. Cir. 1984) ("It is not necessary that the claimed subject matter be described identically, but the disclosure must convey to those skilled in the art that applicant had invented the subject matter later claimed.") (emphasis added). Applicant respectfully asserts that claim 22 already specifies that the target polynucleotide is not labeled during practice of the invention; however, the claim has been amended to clarify this aspect in accordance with the undersigned's telephonic conference with the Examiner.

The methods disclosed in the '896 Chan patent and the '420 Chan patent require a labeled polymer molecule, *i.e.*, a target polynucleotide, and the interaction between the labeled polymer and the labeled enzyme is detected. The method of the subject invention does not require a labeled polymer. Applicant's claimed invention requires only a simple measure of fluorescence of a single molecule in order to determine the sequence of a polynucleotide. There is no need for incorporated nucleotides to be labeled. A key requirement of the Chan patents is that a label must be present on the enzyme and a label must be present on the target polymer. As noted previously, Applicant's claimed method does not require that the target polynucleotide be labeled; claim 22 specifically recites that the target polynucleotide is not labeled. In addition, there is no teaching or suggestion in the Chan patents that the conformational change of an enzyme can be detected using only a fluorescent label on the enzyme, to determine the sequence of a target polymer.

Applicant maintains that the Ha *et al.* reference is even less relevant as it is not concerned with DNA sequencing procedures but is seeking to study protein folding. The general teaching of Ha *et al.* is that a fluorescent label can be used to monitor protein structure at single molecule resolution. The enzyme studied, staphylococcal nuclease, is used only as a model protein with no teaching or suggestion to apply this technique in the field of DNA sequencing.

In regard to the §102 rejection, as the Examiner is aware, in order to anticipate, a single reference must disclose within the four corners of the document each and every element and

limitation contained in the rejected claim. *Scripps Clinic & Research Foundation v. Genentech Inc.*, 18 USPQ2d 1001, 1010 (Fed. Cir. 1991). In regard to the §103 rejections, as the Examiner is also aware, it is well established in patent law that in order to support a *prima facie* case of obviousness, a person of ordinary skill in the art must find both the suggestion of the claimed invention, and a reasonable expectation of success in making that invention, solely in light of the teachings of the prior art. *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Applicants respectfully asserts that the references cited in the Office Action, whether taken alone or in combination, do not teach or suggest each and every element of the claimed invention and do not provide the requisite expectation of success. Accordingly, reconsideration and withdrawal of the rejections under 35 USC §§102 and 103 is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicant's agreement with or acquiescence in the Examiner's position.

In view of the foregoing remarks and amendments to the claims, Applicant believes that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicant invites the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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Registration No. 38,261
Phone No.: 352-375-8100
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Gainesville, FL 32614-2950

DRP/sl

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,908,736 B1

DATED : June 21, 2005

INVENTOR : Daniel Henry Densham

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Columns 8-9,
Lines 67 and 1, "presence of poly nucleotide monomers, the polynucleotide monomers do not" should read --presence of nucleotide monomers, the nucleotide monomers do not--.

Column 9,
Line 13, "infraction" should read --interaction--.

Column 10,
Line 21, "one FRET: fluorescence" should read --one fluorescence--.

MAILING ADDRESS OF SENDER:
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PATENT NO. 6,908,736
No. of add'l. copies

JUL 18 2005

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,908,736 B1

DATED : June 21, 2005

INVENTOR : Daniel Henry Densham

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JUL 18 2005